REMARKS

Amendments

Claim 1, 17-21 and 30 are amended to indicate that Z, Z' and E, together with the N atom, form a piperidinyl ring. Claim 14 is cancelled. In addition, the claims 1 and 21 are amended to delete references to solvates and derivatives.

New claims 38 and 39 are directed to the treatment of certain thromboembolic diseases. See, e.g., page 6, lines 28-34.

Title

In the Office Action it is asserted that the Title is not descriptive. It is argued that the title does not take into account the bipiperidinyl group. While the bipiperidinyl group is part of the elected group, the Restriction Requirement is still being contested. Furthermore, the specification clearly discloses compounds other than bipiperidinyl compounds. The Office Action fails to state the statute or rule that would require a new title directed to only part of the disclosure or a new title limited to an elected group from a Restriction Requirement.

In any event, the title of "Carboxamide Derivatives" is changed to "Piperidinyl Compounds."

Election

Reconsideration of the Restriction is again respectfully requested. In the Office Action of May 21, 2008, the Examiner argues that the variables Z, Z' and E form different ring structures for Groups I and II, and that group T also differs for Groups I and II.

However, applicants did not request withdrawal of the restriction as between Groups I and II. Instead, applicants requested withdrawal of the Restriction as between Groups I and Groups III, IV, and IX (as well as any relevant compounds within group XI) with respect to those compounds in which Z, Z' and E form a piperidine ring.

In the Restriction, applicants' compound genus is divided into 11 Groups, depending on the definitions of the variable groups Q, T and the combination of E, Z, and Z'. As noted in the Restriction, **a Markush grouping (as presented in the instant claims) will satisfy PCT rule 13.2 if the alternatives share a common property or activity and the there is a**

significant common structural element shared by the alternatives.

The compounds share a common activity or property as discussed in applicants' specification. Additional, the alternatives will share a common significant structure, namely a central piperidinyl ring, when Z, Z' and E form a piperidine ring. Thus, applicants again respectfully request that groups III, IV, and IX (as well as any relevant compounds within group XI) be examined with the elected Group I as to those compounds in which Z, Z' and E form a piperidine ring.

Information Disclosure Statement

The references cited in the Information Disclosure Statement filed June 14, 2006 are the references cited in the International Search Report, a copy of which has been filed with the USPTO (See Notice of Acceptance issued March 7, 2007). The Examiner does not explain why the references from the International Search Report are not being considered in this US national Phase application.

With respect to the cited US patent documents, there is no requirement that copies be provided, yet the Examiner did not indicate that the cited US patent documents were considered.

In any event, applicants submit herewith a new Information Disclosure Statement with copies of the foreign patent documents. Consideration of all the documents cited in the Information Disclosure Statement, both US and foreign, is respectfully requested,

Rejection of Claims 1-37 under 35 USC 112, first paragraph

Claims 1-37 are rejected as allegedly being non-enabled with respect to the term "solvates." This rejection is respectfully traversed.

One of ordinary skill in the art upon reading applicants' specification would recognize that applicants' convey the concept of solvates of the claimed compounds. Preparation of solvates can be readily achieved by one of ordinary skill in the art using no more than routine experimentation. In any event, to further prosecution, the claims are amended to delete references to solvates. Withdrawal of the rejection is respectfully requested.

Rejection of Claims 24 and 27-29 under 35 USC 112, first paragraph

Claims 24 and 27-29 are rejected as allegedly being non-enabled with respect to some disorders related to factors VIIIa and Xa. This rejection is respectfully traversed.

Firstly, applicants acknowledge the Examiner's indication that the disclosure is enabling for the treatment of thrombosis. However, since the disclosure is enabling for the treatment of thrombosis, it is unclear why the specification is alleged to be non-enabling for the treatment of other thromboembolic diseases, such as myocardial infarction, arteriosclerosis, inflammation, apoplexy, angina pectoris, restenosis after angioplasty, claudicatio intermittens, venous thrombosis, pulmonary embolism, arterial thrombosis, myocardial ischaemia, unstable angina and strokes based on thrombosis. See diseases recited in claim 27, new claim 39, and page 6, lines 28-34.

In the rejection, reference is made to the so-called Wands factors. It is noted that these factors are used to determine whether undue experimentation is involved. See, *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). However, before the issue of undue experimentation arises, the PTO must present reasons to doubt the veracity of the objective enablement statements presented in an applicants' specification.

In making a lack of enablement rejection, it is the initial burden of the PTO to establish a reason to doubt the truth of the statements presented in the specification concerning enablement. See, e.g., *In re Marzocchi et al.,* 169 USPQ 367, 370 (CCPA 1971). It is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure. In addition, as stated in the *Marzocchi* decision:

> "a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of section 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support" (emphasis in original).

See *In re Marzocchi*, at 369. See also *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995). Thus, all that is required under the statute is **objective** enablement.

The specification provides more that sufficient guidance to objectively enable one of ordinary skill in the art to make and use the claimed compounds and to practice the claimed methods. For example, the specification discloses that the compounds of the invention can exhibit factor Xa-inhibiting properties and thus can be used in treating thromboembolic diseases. Additionally, the specification discloses that the compounds of the invention are inhibitors of factor VIIa, factor IXa, and thrombin in the blood coagulation cascade. See, e.g., page 4, lines 1-12.

Dosages and administration regimes are described at, for example, pages 29-36 of applicants' specification. Procedures for synthesizing compounds of the invention are described at pages 8-9, 22-28, and the Examples, and assays for determining the relative amount of activity of each of the claimed compounds are described at page 5. Additionally, on page 44, IC_{50} values for the inhibition of Factor FXa and factor TF/VIIa are provided for compounds of the invention. Such disclosure provides more than adequate objective enablement for one of ordinary skill in the art to practice the claimed invention without undue experimentation.

Further, the specification discloses that compounds according to the invention can be used for the treatment of tumours, tumour diseases and/or tumour metastases. As noted in the specification, the art recognizes a correlation between tissue factor TF/factor VIIa and the development of various types of cancer [T.Taniguchi and N.R. Lemoine in Biomed. Health Res. (2000), 41 (Molecular Pathogenesis of Pancreatic Cancer), 57-59]. See the discussion at page 6 of applicants' specification. Further evidence of recognition in the art of the antitumour action of TF-VII and factor Xa inhibitors for various types of tumour can be found in articles cited in applicants' specification [K.M. Donnelly et al. in Thromb. Haemost. 1998, 79: 1041-1047; E.G. Fischer et al. in J. Clin. Invest. 104: 1213-1221 (1999); B.M. Mueller et al. in J. Clin. Invest. 101: 1372-1378 (1998); and M.E. Bromberg et al. in Thromb. Haemost. 1999; 82: 88-92].

The rejection does not refute the recognition in the art of the correlation between tissue factor TF/factor VIIa and the development of various types of cancer and of the antitumor action of TF-VII and factor Xa inhibitors for various types of tumour, as evidence

by the above cited references. In light of such recognition, the rejection fails to present any rationale as to why one of ordinary skill in the art would doubt the statements of objective enablement in applicants' specification.

The rejection presents no rationale as to why one of ordinary skill in the art would doubt the objective enablement statements in applicants' disclosure that the compounds of the claimed genus have factor Xa-inhibiting properties factor TF/VIIa-inhibiting properties. Furthermore, using the assays described in the specification, one of ordinary skill in the art can readily determined the relative amount of such activity of any given compound of the claimed genus and be enabled to use the compound in the claimed methods in light of the guidance provided in the specification with respect to dosages, formulations, and modes of administration, and by using no more than routine experimentation. A considerable amount of experimentation is permissible, if it is merely routine, or if the specification provides a reasonable amount of guidance with respect to the direction the experimentation should proceed. *In re Wright,* 999 F.2d 1557, 1561 (Fed. Cir, 1993).

In discussing the Wands factors, the Examiner notes that one of the factors is whether the art is unpredictable. Merely because an art is alleged to be unpredictable does not establish non-enablement. See, e.g., *In re Angstadt*, 190 USPQ 214, 219 (CCPA 1976) in which the art involved (catalysis) was acknowledged to be unpredictable, yet the court still found the disclosure in question to be enabling.

In discussing predictability in the art, the Examiner cites references that disclose that inhibition of factor Xa and factor VIIa are related to treatment of thromboembolic diseases. However, the existence of such articles does not mean the art doesn't also recognize the correlation between tissue factor TF/factor VIIa and the development of various types of cancer, and the antitumor action of TF-VII and factor Xa inhibitors for various types of tumour. See the articles cited above.

It is noted that the rejection acknowledges that one skilled in the art can determine the affinity of the claimed compounds with respect to the factor Xa and factor VIIa receptors. As a result, in light of the guidance in the specification, one of ordinary skill in the art can practice the claimed invention using no more than routine experimentation

The rejection implies that, while assays and assay results are described in the specification, no guidance is provided with respect to the compounds working *in vivo*. It is

noted that examples are not required under the statute. See, for example, the decision in *Marzocchi* wherein the Court expressly stated that:

> The only relevant concern of the Patent and Trademark Office under the circumstances should be over the *truth* of the assertion. The first paragraph of §112 requires nothing more than objective enablement. **How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.** (emphasis added) (*Marzocchi* at 369)

See also MPEP § 2164.02 which acknowledges that compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed.

It is submitted that the courts have routinely held that adequate guidance of pharmacological activity (whether *in vitro* or *in vivo*) is sufficient to support claims of utility, including utility in pharmaceutical applications. See, e.g., *Nelson v. Bowler*, 206 USPQ 881 (CCPA 1980), wherein the court held that tests results on smooth muscle from gerbils and blood pressure modulation in rats established practical utility. In *Cross v. Iizuka*, 224 USPQ 739, the court held that *in vitro* activity of inhibition of thromboxane synthetase satisfied practical utility requirement. As in *Cross v. Iizuka*, applicants' specification and the references cited therein clearly establish the nexus between factor Xa inhibition and treatment of thrombotic conditions and tumors, and the utility of the claimed compounds, as factor Xa and factor VIIa inhibitors, in the treatment of the claimed indications.

As stated in MPEP §2107.03, "evidence of pharmacological or other biological activity of a compound will be relevant to an asserted therapeutic use if there is a reasonable correlation between the activity in question and the asserted utility." As discussed *supra*, such reasonable correlation has been clearly established by the disclosure contained in applicants' own specification and the references cited therein.

In summary, no rationale is provided in the rejection as to why one would doubt that the claimed compounds have the asserted activity. Further, as noted by the Examiner and as evidenced by the articles cited above, compounds having such activity are recognized in the art as candidates in the treatment of the diseases recited in applicants' claims. Additionally, enablement does not require that claimed compounds be subjected to clinical trials, and the performance of well known assays such as described in applicants' specification requires no

more than routine experimentation.

Thus, the rejection fails to set forth reasons as to why one skilled in the art would doubt the veracity of the statements of objective enablement presented in the specification. Further, the rejection fails to present any rationale as to why making and using the invention would require undue experimentation.

In view of the above remarks, it is respectfully submitted that applicants' disclosure provides more than sufficient guidance to objectively enable one of ordinary skill in the art to make and use the claimed invention with no more than routine experimentation. Withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

Rejection of Claims 1-37 under 35 USC 112, first paragraph

Claims 1-37 are rejected as allegedly being indefinite with respect to the term "derivatives" and "cancer." This rejection is respectfully traversed.

The rejection asserts that the terms "derivatives" and "cancer" can be broad. Even if this assertion were true, it is by now well settled law that breadth is not indefiniteness. See, e.g., *In re Gardner et al.*, 166 USPQ 138 (CCPA 1970). Moreover, the term "derivatives" as recited in applicants' claims are more than sufficiently definite when the claim language is read in light of the specification. As for cancer, applicants' claims do not recite this term. Claim 27 does refer to tumors, and one of ordinary skill in the art can readily understand this well know term. Nothing in the rejection suggests otherwise.

In view of the above remarks, withdrawal of the rejection is respectfully requested.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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